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THE POTENTIAL ASSOCIATION OF LUNG CANCER WITH PASSIVE SMOKING

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The potential association of lung cancer with passive smoking has been studied epidemiologically, clinically, and with mathematical models. There have been both positive and negative studies, such that the association is still considered a potential rather than probable one. These studies, and the mathematical models, indicate that major factor in determining the relationship is the dose, and that more research is required to determine the dose side of the dose-response relationship.

Introduction

There has been a growing interest in the potential of passive (or involuntary) smoking as cause of lung cancer (Lebowitz and Apostolides, 1982). This concern is based on chemical analysis of sidestream and mainstream smoke, experiments on the effects of tobacco smoke constituents *in vitro* and *in vivo*, and some recent epidemiological evidence which may link involuntary smoking in spouses to lung cancer mortality. Since the average person spends the great majority of time indoors, it is assumed that there is a large potential for exposure to tobacco smoke generated by others (NRC, 1981).

Exposure Factors

Of the various chemicals derived from tobacco smoke, four of great concern are polycyclic aromatic matter (POM) expressed as benzo(*a*)pyrene (BaP), dimethylnitrosamines, dimethyl benz-anthracene (DMBA) and alpha-emitting radionuclides, mostly polonium 210. Comparisons of mainstream and sidestream smoke have been made by several authors (Brunneman and Hoffman, 1978; Rylander, 1974, 1984; Schmeltz *et al.*, 1975; U.S. Surgeon General, 1980). Further, at least some POM originates from other indoor sources, such as food cooking, wood burning, and other combustions (NRC, 1981). Radiation dosage does occur from cigarettes (Martell, 1974; Little *et al.*, 1965; Radford and Hunt, 1964; DiFranza and Winters, 1982); its relative contribution, to that from other sources, is still debatable (Martell, 1983; Jacobi, 1984). It has been difficult to determine the potential effects of nitrosamines or the radon progeny in the normal indoor environment on humans (Bergman and Axelson, 1983; Martel, 1983).

In vitro studies (Medical Perspectives, 1984; NRC, 1972) have shown some increased mutagenic activity of tobacco products. Studies in mice have shown that condensate from the cigarette end has tumor-producting activity greater than that leaving the mouth piece of the cigarette (U.S. Surgeon General, 1982; Wynder and Hoffman, 1967). Other experiments have been reported to show combined effects of air pollution extracts and cigarette smoke condensate when installed in or on tissue in large amounts (Hoegg, 1972). Sister chromated exchange in cultured human lymphocytes is induced by cigarette smoke condensate, though not appreciably by BaP (Hopkin, 1984).

Passive inhalation of cigarette smoke can produce tracheobronchial epithelial dysplasia and metaplasia in animals at high concentrations of smoke (Holland *et al.*, 1963; U.S. Surgeon General, 1982). The relevance to humans can be questioned because of these high levels, at excess of levels encountered by humans (Schmeltz *et al.*, 1975). "''Attempts to induce significant numbers of bronchogenic carcinoma in laboratory animals were negative in spite of major efforts with several species and strains" (U.S. Surgeon General, 1982). Furthermore, human exposure experiments with sidestream smoke in unventilated rooms

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showed that air concentrations of vapor phase and particulate phase substances decreased with their presence, and the exposure of nonsmokers to tobacco smoke under realistic conditions does not appear to produce inhalation of sufficient amounts of tobacco smoke components traditionally (Holland *et al.*, 1963; Hugod *et al.*, 1978). Hiller *et al.* (1982) measured the deposition fraction of environmental tobacco smoke in humans; the mean was 11% (the median was 8%).

Only mathematical models, such as that of Repace and Lowrey (1985), appear to estimate dosage to humans from environmental tobacco smoke that may be carcinogenic. These models are based on mathematical assumptions and calculations that appear to include overestimations (Esmen, 1981). The dose so derived does not reflect estimates based on actual controlled laboratory studies (First, 1984; Hiller *et al.*, 1982; Hinds *et al.* 1983; Jarvis and Russell, 1984; Johnson and Letzel, 1984; Schievelbein and Richter, 1984), as summarized recently by Hiller (1984), and evaluated by a WHO Committee (1983). Actual estimates (First, 1984; Hiller *et al.* 1982, 1985; Hinds *et al.*, 1983; Jarvis and Russell, 1984; Johnson and Letzel, 1984; Schievelbein and Richter, 1984) imply a dosage to the passive smoker of less than 2 (range of 0.1 – 2) cigarettes/day, except in unusual circumstances; these estimates are ten- to one-hundred-fold less than that in the Repace and Lowrey model (1985). Dosage is the key ingredient to the question of association, and it will require further determination.

Epidemiology

Some have opined that involuntary cigarette smoke possibly contributes to the otherwise unexplained phenomena of lung cancer in nonsmokers and differences in lung cancer rates between rural and urban areas (Cooper *et al.* 1968; Hoegg, 1972), though most studies and reviews link this mortality to occupational and other environmental exposures (Cooper *et al.* 1968; Goldsmith and Friberg, 1977; Lippmann and Schlesinger, 1979; Shy *et al.*, 1978; U.S. Surgeon General, 1982).

At least in the United States, lung cancer deaths in nonsmokers have not increased in the last three decades in either sex (Garfinkel, 1981). Studies of the relationship between involuntary smoking and lung cancer have been performed primarily in females who are exposed to the sidestream smoke of their spouses. Females have lower lung cancer rates than males, even in smokers, and the relative risk ratios appear lower for female smokers than male smokers; these differences are thought to be due to differences in age of onset of smoking, of smoking habits, and occupational exposures (U.S. Surgeon General, 1980, p. 114). Although the occupational exposure of women along with their smoking may produce similar rates to those of males under similar circumstances, fewer women have such exposures (U.S. Surgeon General, 1980, p. 179). In general population samples, however, it is more difficult to accurately ascertain smoking and other exposures in women, especially in traditional societies.

Prospective Population Studies

In a recent study in Japan (Hirayama, 1981), nonsmoking wives of smoking husbands were claimed to have a higher risk of dying from lung cancer than nonsmoking wives of nonsmoking husbands. This study followed 91,540 nonsmoking wives age 40 and older for 14 yr (1966–1979). Husband's age (40–59, 60+) or occupation (agriculture or other) were used to standardize mortality rates for lung cancer and were compared depending on the smoking habits of the husbands; standardization was not on the wives ages or occupations. A relative risk ratio of 2 (1.90–2.36) in nonsmoking wives of heavy smoking husbands was found and was considered significant by the Mantel-extension chi two tailed test; it has not been resolved whether the statistical test was performed correctly. A re-analysis of the data (Harris and DuMouchel, 1981) used a chi-square test statistic for the disaggregated data. Estimating relative risk using maximum likelihood methods for the total set of data also yielded significantly higher rates in the nonsmoking wives with smoking husbands. However, in evaluating the disagregated data several inconsistencies and/or differences of small magnitude were found. For instance, for wives of husbands age 40 – 59 who work elsewhere, the rates for the nonsmoking husband group (10.0) and the rates for the ex- or light-smoking husbands (11.2) are not different; for husbands age 60 or more who work in agriculture, the rates for women with heavy-smoking husbands (35.7) are less than the rates for women with ex- or light-smoking husbands (43.8). As with wives of husbands age 40 – 59 who work elsewhere, wives whose husbands are age 60 or older who work elsewhere who are ex- or light-smokers have rates not distinguishably different from the wives of nonsmoking husbands of that age group or occupational group.

Further problems exist in evaluating the Japanese data, predominantly relating to the actual estimate of exposure to tobacco smoke and of other exposures in females. It may be difficult to correctly ascertain smoking habits of females in this traditional society, as smoking is considered improper for women. Furthermore, indoor exposures to indoor combustion products, especially charcoal or kerosene burning, is likely in Japanese society, and is probably greater in rural females.

Other exposures, either occupational, perri-occupational, ambient, and/or socially related are likely to have clouded the true differences amongst these women (Dore, 1967; Embree, 1939; Vogel, 1971). One Japanese study reported increased cancer related to heating and cooking fuels used especially in rural

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areas, as did one Chinese study (Leung, 1977); another Chinese study found no such effect (MacLennan *et al.*, 1977). It is difficult to ascertain how much time each group of women spends with their smoking or nonsmoking husbands. It is also difficult to determine the effects of ventilation in these homes on the exposure level; it may be that the women in the agriculture areas have homes with more ventilation as well as infiltration of pesticides and other substances. These problems persist because of other determinants of exposure, determinants of socioeconomic status, and the urban rural differences have not been characterized sufficiently, despite assumptions made about such differences (Hammond and Selikoff, 1981; Hirayama, 1981). Further, the major differences seen in wives of husbands age 40 to 59 in agriculture was based on only 3 female deaths in wives of nonsmoking husbands; further estimates of risk, depending on one's assumptions, could lead to different results (Rutsch, 1981).

Finally, other smoking-related causes of death were not significantly different between passive and nonpassive smoking wives. Subsequent letters to the editor of the *British Medical Journal* have been contradictory. Dosage estimates, as shown by the 1984 International Workshop, have been incorrect.

One study in the United States has been analyzed to determine the possible influence of husbands smoking on the mortality experience of nonsmoking wives (Garfinkel, 1981). Adjusted lung cancer deaths among women with nonsmoking husbands matched with women with smoking husbands were not significantly higher in the first group than in the latter groups. The adjusted relative risk ratio for wives with husbands who smoked a pack or more per day was only 1.04. There is no serious disease in the women at the onset of this study. The relationship between the death certificate cause of death and that in the medical records in females was only 83%, indicating possible biases in this study and in other studies of mortality; this bias may be greater for females, as the death certificates and medical records match more closely for males. Only 41% of husbands' smoking was at home. The fact that mortality ratios for light smokers compared to nonsmokers is nearly 5 to 1 in the United States compared to 2 to 1 in Japan would indicate that one would be more likely to see the effects of involuntary smoking in the United States. However, it appears unlikely the wives with husbands who smoke heavily can have mortality ratios that approach those of regular cigarette smokers (Garfinkel, 1984). Thus, the Japanese study (and Greek study, below) may have possible biases in selection or in measurement (Garfinkel, 1984; Rylander, 1984). Garfinkel reported (1984) that their autopsy studies have indicated no atypical cells in the 47 nonsmokers studies. They are starting a new chohort study of 1.2 million people, in which more accurate exposure information will be obtained (Garfinkel, 1984).

Knoth *et al.* (1984) studied 59 females with bronchogenic carcinoma in Germany. The proportion who were nonsmoking spouses of smokers (61.5%) indicated a risk 3 times that based on smoking males. This indicates that there is a high likelihood of misclassification/bias in this study.

Gillis *et al.* (1984) have preliminary results from a cohort study of 16,000 in 2 urban communities in West Scotland. It was shown that cancer incidence and mortality may inconsistently be associated with some small but nonsignificant increase in risk in nonsmoking female spouses of smoking husbands.

There is a major problem in the phenomenological use of data on epidemiological Seventh Day Adventists (SDAs) in mathematical models (Repace and Lowrey, 1985). Generalizations based on SDAs are unjustified as they are a distinctly different group of individuals (compared to a random sample of the general population); they have different lifestyles in addition to different smoking habits. Epidemiologically, Repace and Lowrey (1985) use insufficient methods to control for differences in age and other confounding factors (Friedman *et al.*, 1983; Garfinkel, 1984; Roth, 1981; WHO, 1982; WHO/EURO, 1983).

As Rylander has indicated (1984), none of the cohort studies were designed to study this relationship. In fact, Friedman *et al.* (1983) showed the high rates of misclassification of smoking by spouses, which would over-estimate risk. Garfinkel (1984) has confirmed this misclassification bias. It is difficult to obtain complete information on passive smoking in nonsmoking women. An epidemiological study has to be designed specifically to measure their exposure as accurately as possible, and this is difficult to do. Furthermore, the long-term effects of passive smoking is difficult to establish because of the problems in classification and because of other exposures and/or previous exposures (such as in previously married women); marriage to a smoker is not equivalent to exposure, and other factors may mask important differences.

Case-Control Studies

Case-control studies are meant to measure relative risk (not true probability) and generate hypotheses (not definitive results).

Garfinkel (1984) reported on a recent attempt to do a case-control study. He indicated that half of the primary lung cancer cases were misdiagnosed (by histology) and half of the nonsmokers were current or ex-smokers by their own report (Garfinkel, 1984). When this study was completed (Garfinkel *et al.* 1985), they had 134 cases, 90 with home exposure. Their relative risk ratio by the number of cigarettes the husband smoked in the home was 1.31 overall and over 2.0 for

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more than 1 pack per day, both significant. Both are lower than that for light smokers.

Another case-control study (Sandler *et al.*, 1985) found no significant increase in lung cancer risk but found increases in non-tobacco-related cancers, that is, those normally used as positive controls for reasons of internal reliability and validity (i.e., the study is considered unreliable if the positive control shows an association and invalid if it is significant but the cases—lung cancer—are not). Other methodological and ascertainment problems might explain the gaffe.

A case-control study in Greece (Trichopoulos *et al.* 1981) compared spouses' smoking habits of female lung cancer patients with spouses' smoking habits of other female patients, after excluding smoking females. As indicated by the authors, having only 39 married nonsmoking females in the lung cancer group did not enable them to draw strong conclusions about their odd ratios. Furthermore, only about one-fourth of the lung cancer cases had histological conformation. The controls were matched on their occupation, age, education level, urban/rural residence, and duration of marriage, but were not matched on residence (*vis-à-vis* ambient exposures), other exposures, husband's occupation, or other factors of indoor exposure. It was noted that among the original set of female cases and female controls that the female cases smoked more, as expected, but the relative risk ratio of smoking cases appeared similar to the relative risk ratio of the nonsmoking married females with smoking spouses. These ratios were corrected in subsequent publications (Heller, 1983; Trichopoulos, 1984). Again the ascertainment bias of smoking in females in a somewhat traditional society is possible. The personal habits of the various groups of women are unknown, although others (Hammond and Selikoff, 1981) believe that they are such as to make the estimates of the differences conservative.

Other factors that would affect the exposure to the husband's smoking, such as ventilation in the home, and the time spent with the husband, is unavailable. Since this was a case control study with limited information about co-linear variables or intervening variables, it would take a prospective study in the community with better data collection to insure a better estimate of the probability of risk. Furthermore, such a study would avoid observer bias produced by using only one physician and the need to only one control group (Hammond and Selikoff, 1981). With a prospective study, there is a possibility of better histological conformation, including inclusion of adenocarcinomas which the investigators presently excluded; more recent investigations indicate that all four major histological types, including adenocarcinoma, are related to cigarette smoking (U.S. Surgeon General, 1980, p. 113).

Chan and Fung (1982) have reported on a hispital-based case-control study in Hong Kong. Comparing 83 female lung cancer cased to 139 females controls showed no difference in the proportions of each group with smoking husbands. Koo *et al.* (1985) performed a case control study in Hong Kong, in which the analysis of all histological types in never-smoking females did not reveal any significant increase in relative risk from passive smoking. Other environmental factors which encourage bronchial irritation are suspected. They found histological typing responsible for misclassification and biased risk values between active and passive smoking seen in other studies.

Correo *et al.* (1983) published a case-control study of lung cancer in nonsmoking men and women classified by the number of cigarettes smoked per day by their spouses. Relative risks in women was significant only for those with heavy (40+/day) smoking husbands. However, this study was based on 22 lung cancers in nonsmoking women and 8 in nonsmoking men. They examined whether or not there was an association with parents' smoking habit when they were children as well. No association was found with paternal smoking. There was an elevated risk in smokers whose mothers smoked, after controlling for other variables, but no elevated risk in nonsmokers. No attempts were made to ascertain *post hoc* bias in reporting, nor accuracy of the estimate of exposure.

Kabat and Wynder (1984) reported on 25 nonsmoking men and 53 nonsmoking women classified not only by whether or not their spouse smoked, but also whether or not they were exposed to smoke of others at work or at home. In women there was no increase in risk of lung cancer for any of these three measures. In men there was increased risk of lung cancer in those exposed at work (barely statistically significant), but no increase in risk in those exposed at home or from spouse's smoking. They concluded that more data must be collected before any conclusion can be drawn relating to the effects of passive smoking.

A study based on interviewing the next of kin of deceased cases (Miller, 1984) showed slightly higher rates of all cancer deaths in women with smoking husbands (versus those with nonsmoking husbands) but lower rates of coronary artery disease and other causes in those same women. The odds ratio was calculated incorrectly. Nevertheless, it showed significantly increased cancer deaths in only one of 4 age groups, and as low as 0.4 in another age group; the overall odds ratio was not significant. Examining only nonemployed wives reduced the significant odds ratio to nonsignificance ($X^2 = 0.93$), although the overall ratio was now significant; the latter still requires age adjustment before considered suggestive. Employed wives had an overall odd ratio of 0.8.

Models

Since estimated exposure in passive smokers is between 0.01 – 2 cigarette/day, one could linearily estimate an age adjusted relative cancer risk between

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1.03–1.36. The impact of this on cancer incidence especially in the majority of the range, is considered small (Vutuc, 1983). The difficulty is that we do not know if the dose-response curve is linear (no threshold) or nonlinear (with a threshold), indicating that extrapolation at these low levels of exposure is risky.

The one-hit model of cancer risk is a crude model; it assumes a non-threshold linear dose-response relationship and extrapolation to low doses. As shown by others (Roth, 1981; Albert, 1981; Althshuler, 1981; Caplan *et al.*, 1983; Jacobi, 1984; Luken and Miller, 1977; Radford and St. Clair, 1984; Schnerderman, 1981; Task Force, 1982; Wyzga, 1981), this model overestimates risk from more likely exponential or mulihit models. The model and methods used by Repace and Lowrey (1985) and others do not provide estimates of precision, confidence intervals, or consistency estimates (Beran, 1971; Black, 1970; Luken and Miller, 1977; Smith, 1961), the very statistical bases of estimation procedures.

Discussion

The fundamental dilemmas are (1) basic epidemiological or statistical errors in previous studies which are often ignored by nonepidemiologists (U.S. Surgeon General, 1982, 1984); (2) misclassification of exposure and of lung cancer (Friedman *et al.*, 1983; Garfinkel, 1984); and (3) the problem of dose (Albert, 1983) and exposure-response relationships (Jarvis and Russell, 1984). The biological consequences of smoking require a certain dose over a certain time (Garfinkel, 1984; IARC, 1984; Vutuc, 1984), which if low, may not even be significantly noticed in low doses in large populations (U.S. Surgeon General, 1982). It seems unlikely that passive smoking is responsible for about one-third of the annual lung cancer mortality among U.S. nonsmokers (Repace and Lowrey, 1985). One must recognize also that nonsmokers may have developed lung cancer from other environmental agents: radon progency may account for 5%–30% (most likely 5%–15%) of such mortality (Edling *et al.*, 1984; Hess *et al.*, 1983; Jacobi, 1984; Radford and St. Clair, 1984), and volatile organic compounds (Albert, 1983; NRC, 1972), asbestos (Hirayama, 1981; Holland *et al.*, 1963), and various other environmental factors have been blamed as well. In conclusion, the Repace and Lowrey (1985) estimates of nonsmokers' lung cancer risk from passive smoking is an overstatement.

Lung cancer risk estimated to be twice as high in passive smokers as in nonsmokers not exposed to the smoke of their partner is hardly conceivable because of the absence of cell modifications in the tracheobronchial tract of passive smokers (Garfinkel, 1984). Thus, the problem of passive smoking may be too small to measure in population studies (Garfinkel, 1981; Rylander, 1984). A 1983 International workgroup (Rylander, 1984) agreed that there was sufficient association to support further research. Further case-referent approaches could be considered. Further research should measure actual exposure to environmental tobacco smoke, as recently requested by NCI (NCI RFA 84-Ca-14). It should consider the contributions of specific agents thought to produce cancer, such as nitrosamines and polycyclic hydrocarbons. Further research should include other possible carcinogenic agents and confounding factors, such as occupational exposure, other exposures of the nonsmoking household members, social status and other risk variables.

Conclusion

One must weigh several factors before we claim certain causality that smoking by parents, spouses, friends, and workmates will definitely give nonsmokers cancer. As previous public health experience has shown when one lacks causal links, anxiety increases, as do its sequaelae, as does cost, with increasing iatrogenic disease (i.e., induced by the ""healer") and little benefit in actually preventing overt disease, disability and premature mortality. However, once causality has been shown, we must act quickly to prevent disease. In the interim, we should work to prevent active smoking.

The U.S. Surgeon General's report 1982 (p. 249) stated: ""Although the currently available evidence is not sufficient to conclude that passive or involuntary smoking causes lung cancer in nonsmokers, the evidence does raise concern about a possible serious public health problem." At present, it can only be concluded that it will require further investigation before the estimated probability of risk can be determined.

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